<110> SZKUDLINSI, Mariusz W.
WIENTRAUB, Bruce D.

<120> Follicle Stimulating Hormone Superagonists

<130> 056815-5001-WO

<150> US 60/554,419
<151> 2004-03-19

<160> 24

<170> PatentIn version 3.3

<210> 1
<211> 92
<212> PRT
<213> Homo sapiens

<400> 1

Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr Leu Gln Glu Asn Pro
1 5 10 15

Phe Phe Ser Gln Pro Gly Ala Pro Ile Leu Gln Cys Met Gly Cys Cys
20 25 30

Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser Lys Lys Thr Met Leu
35 40 45

Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys Cys Val Ala Lys Ser
50 55 60

Tyr Asn Arg Val Thr Val Met Gly Gly Phe Lys Val Glu Asn His Thr
65 70 75 80

Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys Ser
85 90

<210> 2
<211> 111
<212> PRT
<213> Homo sapiens

<400> 2

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro
50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr
65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
100 105 110

<210> 3
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino terminal extension; potential glycosylation recognition site

<400> 3

Ala Asn Ile Thr Val
1 5

<210> 4
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino terminal extension; potential glycosylation recognition site

<400> 4

Ala Asn Ile Thr Val Asn Ile Thr Val
1 5

<210> 5
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Negatively charged amino acid insert to modify protein half-life

<400> 5

Gly Glu Phe Thr
1

<210> 6
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Negatively charged amino acid insert to modify protein half-life

<400> 6

Gly Glu Phe Thr Thr
1 5

<210> 7
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> FSH segment with negatively charged amino acid insert to modify protein half-life

<400> 7

Ala Asp Pro Gly Glu Phe Thr Val Gln Asp Cys
1 5 10

<210> 8
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> FSH segment with negatively charged amino acid insert to modify protein half-life

<400> 8

Ala Asp Pro Gly Glu Phe Thr Thr Gln Asp Cys
1 5 10

<210> 9
<211> 97
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 9

Ala Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr
1 5 10 15

Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala Pro Ile Leu Gln
20 25 30

Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser
35 40 45

Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys
50 55 60

Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly Gly Phe Lys
65 70 75 80

Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys
85 90 95

Ser

<210> 10
<211> 97
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 10

Ala Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr
1 5 10 15

Leu Gln Arg Asn Pro Phe Phe Ser Arg Pro Gly Ala Pro Ile Leu Gln
20 25 30

Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser
35 40 45

Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys
50 55 60

Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly Arg Phe Lys
65 70 75 80

Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys
85 90 95

Ser

<210> 11
<211> 101
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 11

Ala Asn Ile Thr Val Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys
1 5 10 15

Pro Glu Cys Thr Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala
20 25 30

Pro Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr
35 40 45

Pro Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser
50 55 60

Glu Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met
65 70 75 80

Gly Gly Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys
85 90 95

Tyr Tyr His Lys Ser
100

<210> 12
<211> 101
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 12

Ala Asn Ile Thr Val Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys
1 5 10 15

Pro Glu Cys Thr Leu Gln Arg Asn Pro Phe Phe Ser Arg Pro Gly Ala
20 25 30

Pro Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr
35 40 45

Pro Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser
50 55 60

Glu Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met
65 70 75 80

Gly Arg Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys
85 90 95

Tyr Tyr His Lys Ser
100

<210> 13
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH beta mature peptide sequence

<400> 13

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro
50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Asn Ala Thr
65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
100 105 110

<210> 14
<211> 111

<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH beta mature peptide sequence

<400> 14

Asn Ser Cys Arg Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro
50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Asn Ala Thr
65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
100 105 110

<210> 15
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH beta mature peptide sequence

<400> 15

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Asn Glu Thr Val Arg Val Pro
50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr
65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
100 105 110

<210> 16
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH beta mature peptide sequence

<400> 16

Asn Ser Cys Arg Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Asn Glu Thr Val Arg Val Pro
50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr
65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
100 105 110

<210> 17
<211> 121
<212> PRT
<213> Homo sapiens

<400> 17

Ser Arg Glu Pro Leu Arg Pro Trp Cys His Pro Ile Asn Ala Ile Leu
1 5 10 15

Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr Val Asn Thr Thr
20 25 30

Ile Cys Ala Gly Tyr Cys Pro Thr Met Met Arg Val Leu Gln Ala Val
35 40 45

Leu Pro Pro Leu Pro Gln Val Val Cys Thr Tyr Arg Asp Val Arg Phe
50 55 60

Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val Asp Pro Val Val
65 70 75 80

Ser Phe Pro Val Ala Leu Ser Cys Arg Cys Gly Pro Cys Arg Arg Ser
85 90 95

Thr Ser Asp Cys Gly Gly Pro Lys Asp His Pro Leu Thr Cys Asp His
100 105 110

Pro Gln Leu Ser Gly Leu Leu Phe Leu
115 120

<210> 18
<211> 24
<212> PRT
<213> Homo sapiens

<400> 18

Met Asp Tyr Tyr Arg Lys Tyr Ala Ala Ile Phe Leu Val Thr Leu Ser
1 5 10 15

Val Phe Leu His Val Leu His Ser
20

<210> 19
<211> 18
<212> PRT
<213> Homo sapiens

<400> 19

Met Lys Thr Leu Gln Phe Phe Phe Leu Phe Cys Cys Trp Lys Ala Ile
1 5 10 15

Cys Cys

<210> 20
<211> 20

<212> PRT
<213> Homo sapiens

<400> 20

Met Glu Met Leu Gln Gly Leu Leu Leu Leu Leu Leu Leu Ser Met Gly
1 5 10 15

Gly Ala Trp Ala
20

<210> 21
<211> 692
<212> PRT
<213> Rattus norvegicus

<400> 21

Met Ala Leu Leu Leu Val Ser Leu Leu Ala Phe Leu Gly Thr Gly Ser
1 5 10 15

Gly Cys His His Trp Leu Cys His Cys Ser Asn Arg Val Phe Leu Cys
20 25 30

Gln Asp Ser Lys Val Thr Glu Ile Pro Thr Asp Leu Pro Arg Asn Ala
35 40 45

Ile Glu Leu Arg Phe Val Leu Thr Lys Leu Arg Val Ile Pro Lys Gly
50 55 60

Ser Phe Ala Gly Phe Gly Asp Leu Glu Lys Ile Glu Ile Ser Gln Asn
65 70 75 80

Asp Val Leu Glu Val Ile Glu Ala Asp Val Phe Ser Asn Leu Pro Lys
85 90 95

Leu His Glu Ile Arg Ile Glu Lys Ala Asn Asn Leu Leu Tyr Ile Asn
100 105 110

Pro Glu Ala Phe Gln Asn Leu Pro Ser Leu Arg Tyr Leu Leu Ile Ser
115 120 125

Asn Thr Gly Ile Lys His Leu Pro Ala Val His Lys Ile Gln Ser Leu
130 135 140

Gln Lys Val Leu Leu Asp Ile Gln Asp Asn Ile Asn Ile His Ile Val
145 150 155 160

Ala Arg Asn Ser Phe Met Gly Leu Ser Phe Glu Ser Val Ile Leu Trp

```
                165                 170                 175

Leu Ser Lys Asn Gly Ile Glu Glu Ile His Asn Cys Ala Phe Asn Gly
            180                 185                 190

Thr Gln Leu Asp Glu Leu Asn Leu Ser Asp Asn Asn Asn Leu Glu Glu
        195                 200                 205

Leu Pro Asn Asp Val Phe Gln Gly Ala Ser Gly Pro Val Ile Leu Asp
    210                 215                 220

Ile Ser Arg Thr Lys Val His Ser Leu Pro Asn His Gly Leu Glu Asn
225                 230                 235                 240

Leu Lys Lys Leu Arg Ala Arg Ser Thr Tyr Arg Leu Lys Lys Leu Pro
                245                 250                 255

Asn Leu Asp Lys Phe Val Thr Leu Met Glu Ala Ser Leu Thr Tyr Pro
            260                 265                 270

Ser His Cys Cys Ala Phe Ala Asn Leu Lys Arg Gln Ile Ser Glu Leu
        275                 280                 285

His Pro Ile Cys Asn Lys Ser Ile Leu Arg Gln Asp Ile Asp Asp Met
    290                 295                 300

Thr Gln Ile Gly Asp Gln Arg Val Ser Leu Ile Asp Asp Glu Pro Ser
305                 310                 315                 320

Tyr Gly Lys Gly Ser Asp Met Met Tyr Asn Glu Phe Asp Tyr Asp Leu
                325                 330                 335

Cys Asn Glu Val Val Asp Val Thr Cys Ser Pro Lys Pro Asp Ala Phe
            340                 345                 350

Asn Pro Cys Glu Asp Ile Met Gly Tyr Asn Ile Leu Arg Val Leu Ile
        355                 360                 365

Trp Phe Ile Ser Ile Leu Ala Ile Thr Gly Asn Thr Thr Val Leu Val
    370                 375                 380

Val Leu Thr Thr Ser Gln Tyr Lys Leu Thr Val Pro Arg Phe Leu Met
385                 390                 395                 400

Cys Asn Leu Ala Phe Ala Asp Leu Cys Ile Gly Ile Tyr Leu Leu Leu
                405                 410                 415
```

```
Ile Ala Ser Val Asp Ile His Thr Lys Ser Gln Tyr His Asn Tyr Ala
            420                 425                 430

Ile Asp Trp Gln Thr Gly Ala Gly Cys Asp Ala Ala Gly Phe Phe Thr
        435                 440                 445

Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Ala Ile Thr Leu
    450                 455                 460

Glu Arg Trp His Thr Ile Thr His Ala Met Gln Leu Glu Cys Lys Val
465                 470                 475                 480

Gln Leu Arg His Ala Ala Ser Val Met Val Leu Gly Trp Thr Phe Ala
                485                 490                 495

Phe Ala Ala Ala Leu Phe Pro Ile Phe Gly Ile Ser Ser Tyr Met Lys
            500                 505                 510

Val Ser Ile Cys Leu Pro Met Asp Ile Asp Ser Pro Leu Ser Gln Leu
        515                 520                 525

Tyr Val Met Ala Leu Leu Val Leu Asn Val Leu Ala Phe Val Val Ile
    530                 535                 540

Cys Gly Cys Tyr Thr His Ile Tyr Leu Thr Val Arg Asn Pro Thr Ile
545                 550                 555                 560

Val Ser Ser Ser Ser Asp Thr Lys Ile Ala Lys Arg Met Ala Thr Leu
                565                 570                 575

Ile Phe Thr Asp Phe Leu Cys Met Ala Pro Ile Ser Phe Phe Ala Ile
            580                 585                 590

Ser Ala Ser Leu Lys Val Pro Leu Ile Thr Val Ser Lys Ala Lys Ile
        595                 600                 605

Leu Leu Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe Leu
    610                 615                 620

Tyr Ala Ile Phe Thr Lys Asn Phe Arg Arg Asp Phe Phe Ile Leu Leu
625                 630                 635                 640

Ser Lys Phe Gly Cys Tyr Glu Met Gln Ala Gln Ile Tyr Arg Thr Glu
                645                 650                 655
```

```
Thr Ser Ser Ala Thr His Asn Phe His Ala Arg Lys Ser His Cys Ser
            660                 665                 670

Ser Ala Pro Arg Val Thr Asn Ser Tyr Val Leu Val Pro Leu Asn His
        675                 680                 685

Ser Ser Gln Asn
    690
```

<210> 22
<211> 695
<212> PRT
<213> Homo sapiens

<400> 22

```
Met Ala Leu Leu Leu Val Ser Leu Leu Ala Phe Leu Ser Leu Gly Ser
1               5                   10                  15

Gly Cys His His Arg Ile Cys His Cys Ser Asn Arg Val Phe Leu Cys
            20                  25                  30

Gln Glu Ser Lys Val Thr Glu Ile Pro Ser Asp Leu Pro Arg Asn Ala
        35                  40                  45

Ile Glu Leu Arg Phe Val Leu Thr Lys Leu Arg Val Ile Gln Lys Gly
    50                  55                  60

Ala Phe Ser Gly Phe Gly Asp Leu Glu Lys Ile Glu Ile Ser Gln Asn
65                  70                  75                  80

Asp Val Leu Glu Val Ile Glu Ala Asp Val Phe Ser Asn Leu Pro Lys
                85                  90                  95

Leu His Glu Ile Arg Ile Glu Lys Ala Asn Asn Leu Leu Tyr Ile Thr
            100                 105                 110

Pro Glu Ala Phe Gln Asn Leu Pro Asn Leu Gln Tyr Leu Leu Ile Ser
        115                 120                 125

Asn Thr Gly Ile Lys His Leu Pro Asp Val His Lys Ile His Ser Leu
    130                 135                 140

Gln Lys Val Leu Leu Asp Ile Gln Asp Asn Ile Asn Ile His Thr Ile
145                 150                 155                 160

Glu Arg Asn Ser Phe Val Gly Leu Ser Phe Glu Ser Val Ile Leu Trp
```

165 170 175

Leu Asn Lys Asn Gly Ile Gln Glu Ile His Asn Cys Ala Phe Asn Gly
180 185 190

Thr Gln Leu Asp Ala Val Asn Leu Ser Asp Asn Asn Asn Leu Glu Glu
195 200 205

Leu Pro Asn Asp Val Phe His Gly Ala Ser Gly Pro Val Ile Leu Asp
210 215 220

Ile Ser Arg Thr Arg Ile His Ser Leu Pro Ser Tyr Gly Leu Glu Asn
225 230 235 240

Leu Lys Lys Leu Arg Ala Arg Ser Thr Tyr Asn Leu Lys Lys Leu Pro
245 250 255

Thr Leu Glu Lys Leu Val Ala Leu Met Glu Ala Ser Leu Thr Tyr Pro
260 265 270

Ser His Cys Cys Ala Phe Ala Asn Trp Arg Arg Gln Ile Ser Glu Leu
275 280 285

His Pro Ile Cys Asn Lys Ser Ile Leu Arg Gln Glu Val Asp Tyr Met
290 295 300

Thr Gln Ala Arg Gly Gln Arg Ser Ser Leu Ala Glu Asp Asn Glu Ser
305 310 315 320

Ser Tyr Ser Arg Gly Phe Asp Met Thr Tyr Thr Glu Phe Asp Tyr Asp
325 330 335

Leu Cys Asn Glu Val Val Asp Val Thr Cys Ser Pro Lys Pro Asp Ala
340 345 350

Phe Asn Pro Cys Glu Asp Ile Met Gly Tyr Asn Ile Leu Arg Val Leu
355 360 365

Ile Trp Phe Ile Ser Ile Leu Ala Ile Thr Gly Asn Ile Ile Val Leu
370 375 380

Val Ile Leu Thr Thr Ser Gln Tyr Lys Leu Thr Val Pro Arg Phe Leu
385 390 395 400

Met Cys Asn Leu Ala Phe Ala Asp Leu Cys Ile Gly Ile Tyr Leu Leu
405 410 415

```
Leu Ile Ala Ser Val Asp Ile His Thr Lys Ser Gln Tyr His Asn Tyr
            420                 425                 430

Ala Ile Asp Trp Gln Thr Gly Ala Gly Cys Asp Ala Ala Gly Phe Phe
        435                 440                 445

Thr Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Ala Ile Thr
    450                 455                 460

Leu Glu Arg Trp His Thr Ile Thr His Ala Met Gln Leu Asp Cys Lys
465                 470                 475                 480

Val Gln Leu Arg His Ala Ala Ser Val Met Val Met Gly Trp Ile Phe
                485                 490                 495

Ala Phe Ala Ala Ala Leu Phe Pro Ile Phe Gly Ile Ser Ser Tyr Met
            500                 505                 510

Lys Val Ser Ile Cys Leu Pro Met Asp Ile Asp Ser Pro Leu Ser Gln
        515                 520                 525

Leu Tyr Val Met Ser Leu Leu Val Leu Asn Val Leu Ala Phe Val Val
    530                 535                 540

Ile Cys Gly Cys Tyr Ile His Ile Tyr Leu Thr Val Arg Asn Pro Asn
545                 550                 555                 560

Ile Val Ser Ser Ser Ser Asp Thr Arg Ile Ala Lys Arg Met Ala Met
                565                 570                 575

Leu Ile Phe Thr Asp Phe Leu Cys Met Ala Pro Ile Ser Phe Phe Ala
            580                 585                 590

Ile Ser Ala Ser Leu Lys Val Pro Leu Ile Thr Val Ser Lys Ala Lys
        595                 600                 605

Ile Leu Leu Val Leu Phe His Pro Ile Asn Ser Cys Ala Asn Pro Phe
    610                 615                 620

Leu Tyr Ala Ile Phe Thr Lys Asn Phe Arg Arg Asp Phe Phe Ile Leu
625                 630                 635                 640

Leu Ser Lys Cys Gly Cys Tyr Glu Met Gln Ala Gln Ile Tyr Arg Thr
                645                 650                 655
```

Glu Thr Ser Ser Thr Val His Asn Thr His Pro Arg Asn Gly His Cys
660 665 670

Ser Ser Ala Pro Arg Val Thr Ser Gly Ser Thr Tyr Ile Leu Val Pro
675 680 685

Leu Ser His Leu Ala Gln Asn
690 695

<210> 23
<211> 700
<212> PRT
<213> Rattus sp.

<400> 23

Met Gly Arg Arg Val Pro Ala Leu Arg Gln Leu Leu Val Leu Ala Val
1 5 10 15

Leu Leu Leu Lys Pro Ser Gln Leu Gln Ser Arg Glu Leu Ser Gly Ser
20 25 30

Arg Cys Pro Glu Pro Cys Asp Cys Ala Pro Asp Gly Ala Leu Arg Cys
35 40 45

Pro Gly Pro Arg Ala Gly Leu Ala Arg Leu Ser Leu Thr Tyr Leu Pro
50 55 60

Val Lys Val Ile Pro Ser Gln Ala Phe Arg Gly Leu Asn Glu Val Val
65 70 75 80

Lys Ile Glu Ile Ser Gln Ser Asp Ser Leu Glu Arg Ile Glu Ala Asn
85 90 95

Ala Phe Asp Asn Leu Leu Asn Leu Ser Glu Leu Leu Ile Gln Asn Thr
100 105 110

Lys Asn Leu Leu Tyr Ile Glu Pro Gly Ala Phe Thr Asn Leu Pro Arg
115 120 125

Leu Lys Tyr Leu Ser Ile Cys Asn Thr Gly Ile Arg Thr Leu Pro Asp
130 135 140

Val Thr Lys Ile Ser Ser Ser Glu Phe Asn Phe Ile Leu Glu Ile Cys
145 150 155 160

Asp Asn Leu His Ile Thr Thr Ile Pro Gly Asn Ala Phe Gln Gly Met

```
                 165                 170                 175

Asn Asn Glu Ser Val Thr Leu Lys Leu Tyr Gly Asn Gly Phe Glu Glu
            180                 185                 190

Val Gln Ser His Ala Phe Asn Gly Thr Thr Leu Ile Ser Leu Glu Leu
        195                 200                 205

Lys Glu Asn Ile Tyr Leu Glu Lys Met His Ser Gly Ala Phe Gln Gly
    210                 215                 220

Ala Thr Gly Pro Ser Ile Leu Asp Ile Ser Ser Thr Lys Leu Gln Ala
225                 230                 235                 240

Leu Pro Ser His Gly Leu Glu Ser Ile Gln Thr Leu Ile Ala Leu Ser
                245                 250                 255

Ser Tyr Ser Leu Lys Thr Leu Pro Ser Lys Glu Lys Phe Thr Ser Leu
            260                 265                 270

Leu Val Ala Thr Leu Thr Tyr Pro Ser His Cys Cys Ala Phe Arg Asn
        275                 280                 285

Leu Pro Lys Lys Glu Gln Asn Phe Ser Phe Ser Ile Phe Glu Asn Phe
    290                 295                 300

Ser Lys Gln Cys Glu Ser Thr Val Arg Lys Ala Asp Asn Glu Thr Leu
305                 310                 315                 320

Tyr Ser Ala Ile Phe Glu Glu Asn Glu Leu Ser Gly Trp Asp Tyr Asp
                325                 330                 335

Tyr Gly Phe Cys Ser Pro Lys Thr Leu Gln Cys Ala Pro Glu Pro Asp
            340                 345                 350

Ala Phe Asn Pro Cys Glu Asp Ile Met Gly Tyr Ala Phe Leu Arg Val
        355                 360                 365

Leu Ile Trp Leu Ile Asn Ile Leu Ala Ile Phe Gly Asn Leu Thr Val
    370                 375                 380

Leu Phe Val Leu Leu Thr Ser Arg Tyr Lys Leu Thr Val Pro Arg Phe
385                 390                 395                 400

Leu Met Cys Asn Leu Ser Phe Ala Asp Phe Cys Met Gly Leu Tyr Leu
                405                 410                 415
```

```
Leu Leu Ile Ala Ser Val Asp Ser Gln Thr Lys Gly Gln Tyr Tyr Asn
            420                 425                 430

His Ala Ile Asp Trp Gln Thr Gly Ser Gly Cys Gly Ala Ala Gly Phe
        435                 440                 445

Phe Thr Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Val Ile
    450                 455                 460

Thr Leu Glu Arg Trp His Thr Ile Thr Tyr Ala Val Gln Leu Asp Gln
465                 470                 475                 480

Lys Leu Arg Leu Arg His Ala Ile Pro Ile Met Leu Gly Gly Trp Leu
                485                 490                 495

Phe Ser Thr Leu Ile Ala Thr Met Pro Leu Val Gly Ile Ser Asn Tyr
            500                 505                 510

Met Lys Val Ser Ile Cys Leu Pro Met Asp Val Glu Ser Thr Leu Ser
        515                 520                 525

Gln Val Tyr Ile Leu Ser Ile Leu Ile Leu Asn Val Val Ala Phe Val
    530                 535                 540

Val Ile Cys Ala Cys Tyr Ile Arg Ile Tyr Phe Ala Val Gln Asn Pro
545                 550                 555                 560

Glu Leu Thr Ala Pro Asn Lys Asp Thr Lys Ile Ala Lys Lys Met Ala
                565                 570                 575

Ile Leu Ile Phe Thr Asp Phe Thr Cys Met Ala Pro Ile Ser Phe Phe
            580                 585                 590

Ala Ile Ser Ala Ala Phe Lys Val Pro Leu Ile Thr Val Thr Asn Ser
        595                 600                 605

Lys Ile Leu Leu Val Leu Phe Tyr Pro Val Asn Ser Cys Ala Asn Pro
    610                 615                 620

Phe Leu Tyr Ala Ile Phe Thr Lys Ala Phe Gln Arg Asp Phe Leu Leu
625                 630                 635                 640

Leu Leu Ser Arg Phe Gly Cys Cys Lys Arg Arg Ala Glu Leu Tyr Arg
                645                 650                 655
```

Arg Lys Glu Phe Ser Ala Tyr Thr Ser Asn Cys Lys Asn Gly Phe Pro
660 665 670

Gly Ala Ser Lys Pro Ser Gln Ala Thr Leu Lys Leu Ser Thr Val His
675 680 685

Cys Gln Gln Pro Ile Pro Pro Arg Ala Leu Thr His
690 695 700

<210> 24
<211> 699
<212> PRT
<213> Homo sapiens

<400> 24

Met Lys Gln Arg Phe Ser Ala Leu Gln Leu Leu Lys Leu Leu Leu Leu
1 5 10 15

Leu Gln Pro Pro Leu Pro Arg Ala Leu Arg Glu Ala Leu Cys Pro Glu
20 25 30

Pro Cys Asn Cys Val Pro Asp Gly Ala Leu Arg Cys Pro Gly Pro Thr
35 40 45

Ala Gly Leu Thr Arg Leu Ser Leu Ala Tyr Leu Pro Val Lys Val Ile
50 55 60

Pro Ser Gln Ala Phe Arg Gly Leu Asn Glu Val Ile Lys Ile Glu Ile
65 70 75 80

Ser Gln Ile Asp Ser Leu Glu Arg Ile Glu Ala Asn Ala Phe Asp Asn
85 90 95

Leu Leu Asn Leu Ser Glu Ile Leu Ile Gln Asn Thr Lys Asn Leu Arg
100 105 110

Tyr Ile Glu Pro Gly Ala Phe Ile Asn Leu Pro Gly Leu Lys Tyr Leu
115 120 125

Ser Ile Cys Asn Thr Gly Ile Arg Lys Phe Pro Asp Val Thr Lys Val
130 135 140

Phe Ser Ser Glu Ser Asn Phe Ile Leu Glu Ile Cys Asp Asn Leu His
145 150 155 160

Ile Thr Thr Ile Pro Gly Asn Ala Phe Gln Gly Met Asn Asn Glu Ser

165 170 175

Val Thr Leu Lys Leu Tyr Gly Asn Gly Phe Glu Glu Val Gln Ser His
180 185 190

Ala Phe Asn Gly Thr Thr Leu Thr Ser Leu Glu Leu Lys Glu Asn Val
195 200 205

His Leu Glu Lys Met His Asn Gly Ala Phe Arg Gly Ala Thr Gly Pro
210 215 220

Lys Thr Leu Asp Ile Ser Ser Thr Lys Leu Gln Ala Leu Pro Ser Tyr
225 230 235 240

Gly Leu Glu Ser Ile Gln Arg Leu Ile Ala Thr Ser Ser Tyr Ser Leu
245 250 255

Lys Lys Leu Pro Ser Arg Glu Thr Phe Val Asn Leu Leu Glu Ala Thr
260 265 270

Leu Thr Tyr Pro Ser His Cys Cys Ala Phe Arg Asn Leu Pro Thr Lys
275 280 285

Glu Gln Asn Phe Ser His Ser Ile Ser Glu Asn Phe Ser Lys Gln Cys
290 295 300

Glu Ser Thr Val Arg Lys Val Ser Asn Lys Thr Leu Tyr Ser Ser Met
305 310 315 320

Leu Ala Glu Ser Glu Leu Ser Gly Trp Asp Tyr Glu Tyr Gly Phe Cys
325 330 335

Leu Pro Lys Thr Pro Arg Cys Ala Pro Glu Pro Asp Ala Phe Asn Pro
340 345 350

Cys Glu Asp Ile Met Gly Tyr Asp Phe Leu Arg Val Leu Ile Trp Leu
355 360 365

Ile Asn Ile Leu Ala Ile Met Gly Asn Met Thr Val Leu Phe Val Leu
370 375 380

Leu Thr Ser Arg Tyr Lys Leu Thr Val Pro Arg Phe Leu Met Cys Asn
385 390 395 400

Leu Ser Phe Ala Asp Phe Cys Met Gly Leu Tyr Leu Leu Leu Ile Ala
405 410 415

Ser Val Asp Ser Gln Thr Lys Gly Gln Tyr Tyr Asn His Ala Ile Asp
420 425 430

Trp Gln Thr Gly Ser Gly Cys Ser Thr Ala Gly Phe Phe Thr Val Phe
435 440 445

Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Val Ile Thr Leu Glu Arg
450 455 460

Trp His Thr Ile Thr Tyr Ala Ile His Leu Asp Gln Lys Leu Arg Leu
465 470 475 480

Arg His Ala Ile Leu Ile Met Leu Gly Gly Trp Leu Phe Ser Ser Leu
485 490 495

Ile Ala Met Leu Pro Leu Val Gly Val Ser Asn Tyr Met Lys Val Ser
500 505 510

Ile Cys Phe Pro Met Asp Val Glu Thr Thr Leu Ser Gln Val Tyr Ile
515 520 525

Leu Thr Ile Leu Ile Leu Asn Val Val Ala Phe Phe Ile Ile Cys Ala
530 535 540

Cys Tyr Ile Lys Ile Tyr Phe Ala Val Arg Asn Pro Glu Leu Met Ala
545 550 555 560

Thr Asn Lys Asp Thr Lys Ile Ala Lys Lys Met Ala Ile Leu Ile Phe
565 570 575

Thr Asp Phe Thr Cys Met Ala Pro Ile Ser Phe Phe Ala Ile Ser Ala
580 585 590

Ala Phe Lys Val Pro Leu Ile Thr Val Thr Asn Ser Lys Val Leu Leu
595 600 605

Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe Leu Tyr Ala
610 615 620

Ile Phe Thr Lys Thr Phe Gln Arg Asp Phe Phe Leu Leu Leu Ser Lys
625 630 635 640

Phe Gly Cys Cys Lys Arg Arg Ala Glu Leu Tyr Arg Arg Lys Asp Phe
645 650 655

Ser Ala Tyr Thr Ser Asn Cys Lys Asn Gly Phe Thr Gly Ser Asn Lys
660 665 670

Pro Ser Gln Ser Thr Leu Lys Leu Ser Thr Leu His Cys Gln Gly Thr
675 680 685

Ala Leu Leu Asp Lys Thr Arg Tyr Thr Glu Cys
690 695